Identification by automated screening of a small molecule that selectively eliminates neural stem cells derived from hESCs but not dopamine neurons.

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Public Summary:

Scientific Abstract:
BACKGROUND: We have previously described fundamental differences in the biology of stem cells as compared to other dividing cell populations. We reasoned therefore that a differential screen using US Food and Drug Administration (FDA)-approved compounds may identify either selective survival factors or specific toxins and may be useful for the therapeutically-driven manufacturing of cells in vitro and possibly in vivo. METHODOLOGY/PRINCIPAL FINDINGS: In this study we report on optimized methods for feeder-free culture of hESCs and hESC-derived neural stem cells (NSCs) to facilitate automated screening. We show that we are able to measure ATP as an indicator of metabolic activity in an automated screening assay. With this optimized platform we screened a collection of FDA-approved drugs to identify compounds that have differential toxicity to hESCs and their neural derivatives. Nine compounds were identified to be specifically toxic for NSCs to a greater extent than for hESCs. Six of these initial hits were retested and verified by large-scale cell culture to determine dose-responsive NSC toxicity. One of the compounds retested, amiodarone HCL, was further tested for possible effects on postmitotic neurons, a likely target for transplant therapy. Amiodarone HCL was found to be selectively toxic to NSCs but not to differentiated neurons or glial cells. Treated and untreated NSCs and neurons were then interrogated with global gene expression analysis to explore the mechanisms of action of amiodarone HCl. The gene expression analysis suggests that activation of cell-type specific cationic channels may underlie the toxicity of the drug. CONCLUSIONS/SIGNIFICANCE: In conclusion, we have developed a screening strategy that allows us to rapidly identify clinically approved drugs for use in a Chemistry, Manufacture and Control protocol that can be safely used to deplete unwanted contaminating precursor cells from a differentiated cell product. Our results also suggest that such a strategy is rich in the potential of identifying lineage specific reagents and provides additional evidence for the utility of stem cells in screening and discovery paradigms.